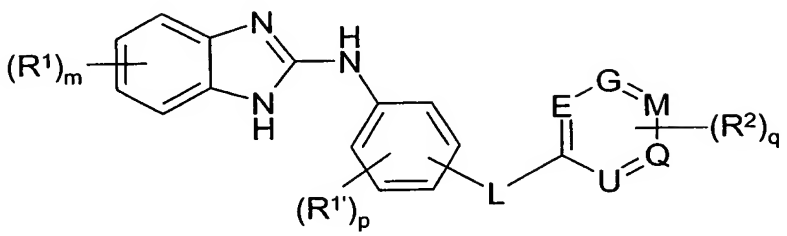
Patent Claims

1. Compounds of the formula I



I

in which

R^1, $R^{1'}$ each, independently of one another, stand for Hal, A, OH, OA, SA, SO_2H, SO_2A, SO_3H, SO_3A, CN, NO_2, NH_2, NHA, NAA', NHCOA, CHO, C(=O)A, COOH, COOA, $CONH_2$, CONHA or CONAA',

L denotes CH_2, CH_2CH_2, O, S, SO, SO_2, NH, NA, C=O or CHOH,

R^2, independently, is selected from the meanings indicated for R^1 and $R^{1'}$ and is preferably, independently, selected from Hal, A, OH, OA, CN, COOH, COOA, $CONH_2$, CONHA or CONAA',

E, G, M,

Q and U each, independently of one another, stand for a C atom or an N atom,

A, A', independently of one another, are selected from unsubstituted or substituted alkyl having 1-10 C atoms, unsubstituted or substituted cycloalkyl having 3-10 C atoms, unsubstituted or substituted alkoxyalkyl having 2-12 C atoms, unsubstituted or substituted aryl having 6-14 C atoms, unsubstituted or substituted arylalkyl having 7-15 C atoms, unsubstituted or substituted, saturated, unsaturated or aromatic heterocyclyl having 2-7 C atoms and 1-3 hetero atoms selected from N, O and S, or unsubstituted or substituted, saturated, unsaturated

or aromatic heterocyclylalkyl having 3-10 C atoms and 1-3 hetero atoms selected from N, O and S,

Hal denotes F, Cl, Br or I, and

m, p, q each, independently of one another, denote 0, 1, 2, 3 or 4,

and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

2. Compounds according to Claim 1, in which in which the radicals

R^1, independently of one another, are selected from A, Hal, CN, COOH, COOA, SO_2A, C(=O)A, NH_2, NHA and NO_2, and

m denotes 1, 2 or 3,

and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

3. Compounds according to Claim 1 in which the radicals

R^1, independently of one another, are selected from methyl, ethyl, CF_3, OCF_3, F, Cl, Br, CN, COOH, $COOCH_3$, $COOCH_2CH_3$, SO_2CH_3, NH_2, $NHCH_3$, $NHCH_2CH_3$, NO_2, thiophen-2-ylcarbonyl, and

m denotes 1, 2 or 3,

and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

4. Compounds according to one or more of Claims 1-3 in which

$R^{1'}$ denotes Hal or A,

p denotes 0 or 1,

and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

5. Compounds according to one or more of Claims 1-4 in which

L denotes O, S or CH_2,

and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

6. Compounds according to one or more of Claims 1-5 in which

R^2 denotes A, COOA, CONHA or $CONH_2$, and

q denotes 0, 1 or 2,

and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

7. Compounds according to one or more of Claims 1-6 in which

R^1, independently of one another, denotes Hal, alkyl, CN, COOH, COOalkyl, SO_2alkyl, NH_2, NHalkyl, C(=O)alkyl, C(=O)heterocyclyl or NO_2,

m denotes 1, 2 or 3, preferably 1 or 2,

$R^{1'}$ denotes Hal or A, preferably Hal or alkyl,

p denotes 0 or 1,

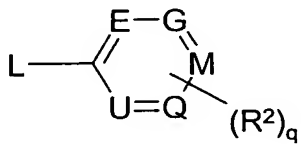
L denotes O, S or CH_2, preferably O or CH_2,

R^2 denotes A, COOalkyl, CONHalkyl or $CONH_2$, and

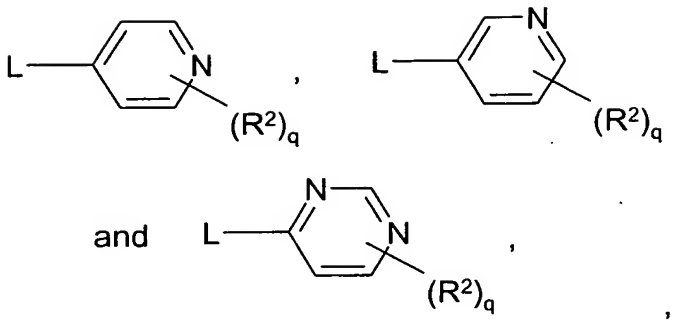
q denotes 0, 1 or 2,

and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

8. Compounds according to one or more of Claims 1-7 in which the group



in formula I is selected from



and

in which L, R^2 and q have the meanings indicated in one or more of Claims 1 to 7,
and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

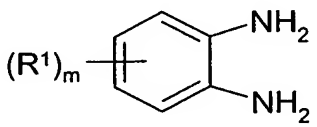
9. Compounds according to one of Claims 1 to 8, selected from the group
(5-chloro-6-trifluoromethyl-1H-benzimidazol-2-yl)[4-(pyridin-4-yloxy)-phenyl]amine;
[4-(pyridin-4-yloxy)phenyl](6-trifluoromethyl-1H-benzimidazol-2-yl)-amine;
(6-methyl-1H-benzimidazol-2-yl)[4-(pyridin-4-yloxy)phenyl]amine;
(5-chloro-4-methyl-1H-benzimidazol-2-yl)[4-(pyridin-4-yloxy)phenyl]-amine;
(4-bromo-6-trifluoromethyl-1H-benzimidazol-2-yl)[4-(pyridin-4-yloxy)-phenyl]amine;
(4-bromo-6-trifluoromethyl-1H-benzimidazol-2-yl)[4-(pyridin-3-yloxy)-phenyl]amine;
(5,6-dimethyl-1H-benzimidazol-2-yl)[4-(pyridin-4-yloxy)phenyl]amine;
(5-chloro-6-trifluoromethyl-1H-benzimidazol-2-yl)[4-(pyridin-3-yloxy)-phenyl]amine;
(5,6-dichloro-1H-benzimidazol-2-yl)[4-(pyridin-4-yloxy)phenyl]amine;
(5,6-dichloro-1H-benzimidazol-2-yl)[4-(pyridin-3-yloxy)phenyl]amine;
(5-chloro-1H-benzimidazol-2-yl)[4-(pyridin-4-yloxy)phenyl]amine;

(5-chloro-1H-benzimidazol-2-yl)[4-(pyridin-3-yloxy)phenyl]amine;
(4-methyl-1H-benzimidazol-2-yl)[4-(pyridin-3-yloxy)phenyl]amine;
(4-chloro-6-trifluoromethyl-1H-benzimidazol-2-yl)[4-(pyridin-4-yloxy)-phenyl]amine;
(4-chloro-6-trifluoromethyl-1H-benzimidazol-2-yl)[4-(pyridin-3-yloxy)-phenyl]amine;
(4,5-dimethyl-1H-benzimidazol-2-yl)[4-(pyridin-4-yloxy)phenyl]amine;
(5-chloro-6-methyl-1H-benzimidazol-2-yl)[4-(pyridin-4-yloxy)phenyl]-amine;
(5-chloro-6-methyl-1H-benzimidazol-2-yl)[4-(pyridin-3-yloxy)phenyl]-amine;
(4,6-bistrifluoromethyl-1H-benzimidazol-2-yl)[4-(pyridin-4-yloxy)-phenyl]amine;
(4,6-bistrifluoromethyl-1H-benzimidazol-2-yl)[4-(pyridin-3-yloxy)-phenyl]amine;
[4-(pyridin-3-yloxy)phenyl](6-trifluoromethyl-1H-benzimidazol-2-yl)-amine;
(6-methyl-1H-benzimidazol-2-yl)[4-(pyridin-3-yloxy)phenyl]amine;
(4,5-dimethyl-1H-benzimidazol-2-yl)[4-(pyridin-3-yloxy)phenyl]amine;
(5-chloro-4-methyl-1H-benzimidazol-2-yl)[4-(pyridin-3-yloxy)phenyl]-amine;
(4-methyl-1H-benzimidazol-2-yl)[4-(pyridin-4-yloxy)phenyl]amine;
(5,6-dimethyl-1H-benzimidazol-2-yl)[4-(pyridin-3-yloxy)phenyl]amine;
(4-bromo-6-trifluoromethyl-1H-benzimidazol-2-yl)[4-(2,6-dimethyl-pyrimidin-4-yloxy)phenyl]amine;
N-methyl-4-[4-(bromotrifluoromethyl-1H-benzimidazol-2-ylamino)-phenoxy]pyridine-2-carboxamide;
2-[4-(pyridin-4-yloxy)phenylamino]-3H-benzimidazole-5-carbonitrile;
[4-(2-amino-6-methylpyrimidin-4-yloxy)phenyl](4-bromo-6-trifluoro-methyl-1H-benzimidazol-2-yl)amine;
(4-chloro-6-trifluoromethyl-1H-benzimidazol-2-yl)[4-(2,6-dimethyl-pyrimidin-4-yloxy)phenyl]amine;

[4-(2-amino-6-methylpyrimidin-4-yloxy)phenyl](4-chloro-6-trifluoromethyl-1H-benzimidazol-2-yl)amine;
(6-nitro-1H-benzimidazol-2-yl)[4-(pyridin-4-yloxy)phenyl]amine;
methyl 2-[4-(pyridin-4-yloxy)phenylamino]-3H-benzimidazole-5-carboxylate;
2-[4-(pyridin-4-yloxy)phenylamino]-3H-benzimidazole-5-carboxylic acid;
methyl 7-methanesulfonyl-2-[4-(pyridin-4-yloxy)phenylamino]-3H-benzimidazole-5-carboxylate;
(4-fluoro-6-trifluoromethyl-1H-benzimidazol-2-yl)[4-(pyridin-4-yloxy)-phenyl]amine;
[4-(2,6-dimethylpyrimidin-4-yloxy)phenyl](4-fluoro-6-trifluoromethyl-1H-benzimidazol-2-yl)amine;
[4-(2-amino-6-methylpyrimidin-4-yloxy)phenyl](4-fluoro-6-trifluoromethyl-1H-benzimidazol-2-yl)amine;
N-methyl-4-{4-[6-(1-thiophen-2-ylmethanoyl)-1H-benzimidazol-2-yl-amino]phenoxy}pyridine-2-carboxamide;
N^2-[4-(pyridin-4-yloxy)phenyl]-3H-benzimidazole-2,5-diamine;
and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

10. Process for the preparation of compounds of the formula I according to Claims 1-9 and pharmaceutically usable derivatives, solvates and stereoisomers thereof, characterised in that

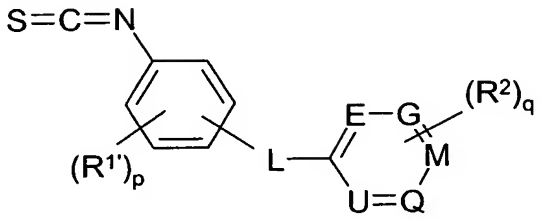
a compound of the formula II



II

in which R^1 and m have the meanings indicated in Claim 1,

is reacted with a compound of the formula III



III

in which $R^{1'}$, L, E, G, M, Q, U, R^2 and q have the meanings indicated in Claim 1,

if desired the compound of the formula I is isolated, and/or a base or acid of the formula I is converted into one of its salts.

11. Medicaments comprising at least one compound according to one of Claims 1 to 9 and/or pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios, and optionally excipients and/or adjuvants.

12. Use of compounds according to one of Claims 1 to 9, and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios, for the preparation of a medicament for the treatment of diseases in which the inhibition, regulation and/or modulation of kinase signal transduction plays a role.

13. Use according to Claim 12, where the kinases are selected from the group of tyrosine kinases and Raf kinases.

14. Use according to Claim 13, where the tyrosine kinases are TIE-2.

15. Use according to Claim 12 of compounds according to Claim 1, and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios, for the preparation of a medicament for the treatment of diseases, which are influenced by inhibition of tyrosine kinases by the compounds according to one of Claims 1 to 9.

16. Use according to Claim 15 for the preparation of a medicament for the treatment of diseases which are influenced by inhibition of TIE-2 by the compounds according to one of Claims 1 to 9.

17. Use according to Claim 15 or 16, where the disease to be treated is a solid tumour.

18. Use according to Claim 17, where the solid tumour originates from the group brain tumour, tumour of the urogenital tract, tumour of the lymphatic system, stomach tumour, laryngeal tumour and lung tumour.

19. Use according to Claim 17, where the solid tumour originates from the group monocytic leukaemia, lung adenocarcinoma, small cell lung carcinomas, pancreatic cancer, glioblastomas and breast carcinoma.

20. Use according to Claim 15 or 16 for the treatment of a disease in which angiogenesis is implicated.

21. Use according to Claim 20, where the disease is an ocular disease.

22. Use according to Claim 15 or 16 for the treatment of retinal vascularisation, diabetic retinopathy, age-induced macular degeneration and/or inflammatory diseases.

23. Use according to Claim 22, where the inflammatory disease originates from the group rheumatoid arthritis, psoriasis, contact dermatitis and delayed hypersensitivity reaction.

24. Use according to Claim 15 or 16 for the treatment of bone pathologies, where the bone pathology originates from the group osteosarcoma, osteoarthritis and rickets.

25. Medicaments comprising at least one compound according to Claim 1 and/or pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios, and at least one further medicament active ingredient.

26. Set (kit) consisting of separate packs of
(a) an effective amount of a compound according to Claim 1 and/or pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios,
and
(b) an effective amount of a further medicament active ingredient.

27. Use of compounds according to Claim 1 and/or physiologically acceptable salts and solvates thereof for the preparation of a medicament for the treatment of solid tumours, where a therapeutically effective amount of a compound according to one of Claims 1 to 9 is administered in combination with a compound from the group 1) oestrogen receptor modulator, 2) androgen receptor modulator, 3) retinoid receptor modulator, 4) cytotoxic agent, 5) antiproliferative agent, 6) a prenyl-protein transferase inhibitor, 7) HMG-CoA reductase inhibitor, 8) HIV protease inhibitor, 9) reverse transcriptase inhibitor and 10) another angiogenesis inhibitor.

28. Use of compounds according to one of Claims 1 to 9 and/or physiologically acceptable salts and solvates thereof for the preparation of a medicament for the treatment of solid tumours where a therapeutically effective amount of a compound according to one of Claims 1 to 9 is administered in combination with radiotherapy and a compound from the group 1) oestrogen receptor modulator, 2) androgen receptor modulator, 3) retinoid receptor modulator, 4) cytotoxic agent, 5) antiproliferative agent, 6) prenyl-protein transferase inhibitor, 7) HMG-CoA reductase inhibitor, 8) HIV protease inhibitor, 9) reverse transcriptase inhibitor and 10) another angiogenesis inhibitor.

29. Use according to Claim 12, 13 or 14, for the preparation of a medicament for the treatment of diseases which are based on disturbed TIE-2 activity,
where a therapeutically effective amount of a compound according to one of Claims 1 to 9 is administered in combination with a growth-factor receptor inhibitor.

30. Use according to Claim 12 or 13 of compounds according to Claim 1, and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios,
for the preparation of a medicament for the treatment of diseases which are caused, mediated and/or propagated by Raf kinases.

31. Use according to Claim 30, where the Raf kinase is selected from the group consisting of A-Raf, B-Raf and Raf-1.

32. Use according to Claim 30, where the diseases are selected from the group of the hyperproliferative and non-hyperproliferative diseases.

33. Use according to Claim 30 or 32, where the disease is cancerous.

34. Use according to Claim 30 or 32, where the disease is non-cancerous.

35. Use according to Claim 30, 32 or 34, where the non-cancerous diseases are selected from the group consisting of psoriasis, arthritis, inflammation, endometriosis, scarring, benign prostatic hyperplasia, immunological diseases, autoimmune diseases and immunodeficiency diseases.

36. Use according to one of Claims 30, 32 or 33, where the diseases are selected from the group consisting of brain cancer, lung cancer, squamous cell cancer, bladder cancer, gastric cancer, pancreatic cancer, hepatic cancer, renal cancer, colorectal cancer, breast cancer, head cancer, neck cancer, oesophageal cancer, gynaecological cancer, thyroid cancer, lymphoma, chronic leukaemia and acute leukaemia.